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Report

Distinct incidence patterns among *in situ* and invasive breast carcinomas, with possible etiologic implications

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Key words: age-specific breast cancer incidence rates, breast carcinoma *in situ*, estrogen receptor expression

Summary

Background. Incidence patterns are well-established for invasive breast carcinoma (InvBC) overall and for InvBC defined by estrogen receptor (ER) expression, but are not as well-defined for breast carcinoma *in situ* (CIS).

Methods. We, therefore, examined and compared the incidence patterns for CIS and InvBC in the SEER program to define these patterns and to generate etiologic hypotheses. Data were stratified by age < 50 and ≥ 50 years to approximate menopause.

Results. During the years 1973–2000, annual age-adjusted incidence rates rose 660% for CIS and 36% for InvBC, with the most rapid increases occurring in women age ≥50 years. Age-specific incidence rate curves for CIS increased until age 50 years, and then flattened, irrespective of ER expression. On the other hand, rates for InvBC overall and for InvBC defined by ER-positive expression increased continuously with aging, whereas rates for InvBC defined by ER-negative expression flattened after 50 years. Age frequency distribution for CIS and for ER-negative InvBC demonstrated bimodal populations, with a predominant early onset peak incidence at age 50 years. Age frequency distribution for ER-positive InvBC showed bimodal populations with a predominant late-onset mode at age 71 years.

Conclusion. Over the last three decades, age-adjusted incidence trends differed for CIS and InvBC in the United States, possibly due to screening mammography and/or etiologic diversity. Indeed, age-specific incidence patterns suggested that carcinogenic events operating early in reproductive life had greater impact upon CIS and InvBC defined by ER-negative expression than upon InvBC overall and InvBC defined by ER-positive expression.

Introduction

In previous population-based studies, we examined incidence patterns for invasive breast carcinoma (InvBC) defined by hormone receptor expression [1,2], major racial groups [2–5], different clinicopathologic subtypes [6–8], and male gender [9]. Age-specific incidence rates for InvBC on the whole generally increased rapidly until age 50 years, and then continued to rise at a slower rate, as originally described by Johannes Clemmesen in 1948 [10]. However, the overall pattern for InvBC varied by hormone receptor expression, race, clinicopathologic class, and gender [1–9,11].

We speculated that incidence patterns for breast carcinomas *in situ* (CIS) might also vary by demographic and tumor characteristics. However, these population-based patterns have not been well-established for CIS. We, therefore, examined incidence trends, age-specific incidence rates, age frequency distribution-at-diagnosis, and incident tumor characteristics among CIS and InvBC cases in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer

Institute (NCI) (November 2002 submission, [12]) to define these patterns and to develop etiologic hypotheses.

Material and methods

We obtained CIS and InvBC records from SEER's 9 original population-based registries: Connecticut, Hawaii, Iowa, Utah, and New Mexico as well as the metropolitan areas of San Francisco, Detroit, Atlanta, and Seattle-Puget Sound. The SEER program began in 1973 but did not record incident tumor size, lymph nodal status and nuclear grade until 1988, and did not collect hormone receptor data until 1990. We adopted age 50 years as our surrogate measure for menopause.

Nuclear histologic grading conformed to the International Classification of Diseases for Oncology-2nd edition (ICDO-2) [13]. We combined grade I (well differentiated) with II (moderately differentiated) and grade III (poorly differentiated) with IV (undifferentiated) into low and high tumor grades, respectively. ICDO-2 codes also defined three distinct architectural subtypes for CIS, including duct non-comedo (DCIS non-comedo; ICDO-2 codes 8010–8011, 8140–8141, 8500), duct comedo (DCIS comedo; ICDO-2 codes 8501), and lobular carcinomas (LCIS; ICDO-2 codes 8520–8521).

Because no centralized laboratory was used to determine hormone receptor status, each SEER registry coded estrogen and progesterone receptors as positive, negative, missing, borderline, or unknown. We combined missing, borderline, and unknown data into one group, designated as hormone receptor unknown.

Incidence rates with standard errors (SE) were calculated using SEER stat 5.0.20, age-adjusted to the 2000 US standard, and expressed per 100,000 woman-years [12]. Annual age-adjusted incidence rates were plotted on a log-linear graph to show temporal changes from 1973 to 2000. Age-specific incidence rates were charted on a log–log scale [14]. Age-frequency density function was plotted as previously described [1,5]. Briefly, the age-frequency density function represented "smoothed" estimates of the age-at-diagnosis frequency histogram where the area under the plot included 100% of breast cancer cases (density value $\times$ 100 = percent of breast cancer cases).

Results

The SEER program collected data for 430,454 female breast cancer cases diagnosed during the years 1973–2000. There were 49,326 records with CIS and 381,128 with InvBC. Median ages-at-diagnosis were 59 and 62 years for CIS and InvBC, respectively. CIS incidence rates rose 660% from 4.3 to 32.7 per 100,000 woman-years during the last three decades, with the most rapid increases occurring during the 1980s (Figure 1a). In contrast to CIS, rates for InvBC increased only 36% during 1973–2000, i.e., from 99 to 135 per 100,000 woman-years.

Over this same time period, rates increased less rapidly among younger than among older women for both CIS and InvBC cases (charts not shown). That is, CIS rates increased 304% and 989% among women <50 and ≥ 50 years, while InvBC rates increased 10.5% and 48% among women <50 and ≥ 50 years of age. Rates for ductal and lobular CIS (DCIS and LCIS) were parallel until 1990, and then flattened for LCIS but continued to rise for DCIS (Figure 1a). Most DCIS had a non-comedo architectural type (79%).

Given the striking temporal trends for CIS and InvBC during the 1980s (Figure 1a), we compared age-specific incidence rates before (1973–1980) and after (1990–2000) widespread mammographic screening. Before widespread screening mammography (1973–1980, Figure 1b), CIS age-specific rates increased rapidly until age 50 years, then declined and plateaued. After widespread screening mammography (1990–2000, Figure 1c), CIS age-specific rates rose rapidly until age 50 years, and then flattened. In contrast to CIS, InvBC rates increased rapidly until age 50 years, and then continued to rise at a slower rate for older women, irrespective of time period (Figure 1b and c).

Table 1 compared certain patient and tumor characteristics for CIS and InvBC during the time period that SEER collected these data, i.e., 1990–2000. There were 35,347 cases with CIS and 188,561 with InvBC. Relative risks were expressed as incidence rate ratios (RR), where the incidence rate for a referent characteristic was assigned the RR of 1.0 (Table 1). RR for black compared to white race was 0.9 for both CIS and InvBC. RR for duct comedo compared to duct non-comedo was greater for CIS (RR = 0.4) than for InvBC (RR = 0.03). Notably, incidence rates for comedocarcinomas were 71% greater for CIS than

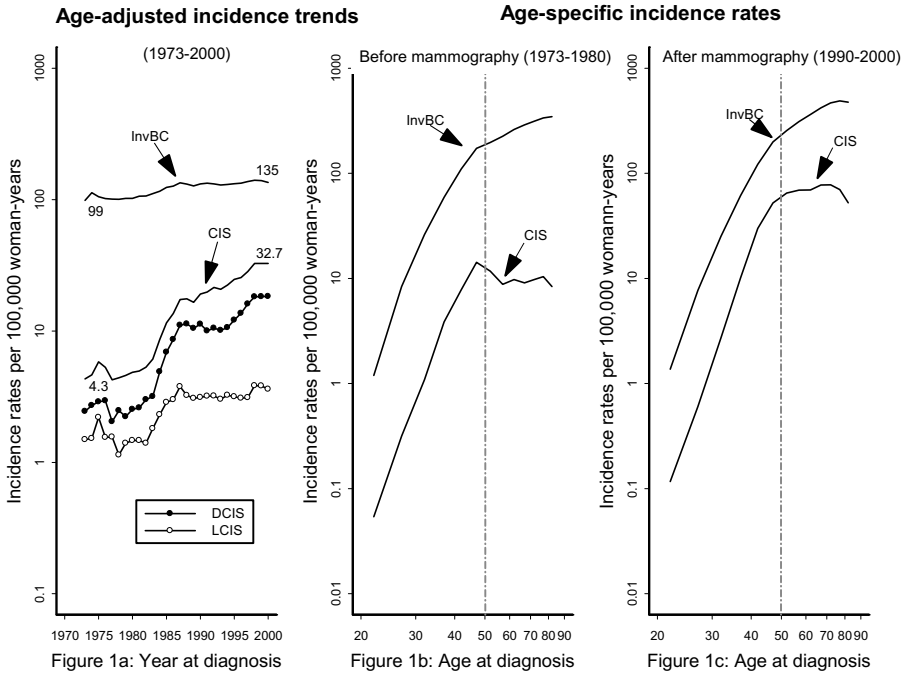

Figure 1. Age-adjusted (2000 US standard) breast cancer incidence trends and age-specific incidence rates among carcinoma *in situ* (CIS) and invasive breast carcinoma (InvBC) cases diagnosed during the years 1973–2000. (a) Age-adjusted trends for InvBC, CIS, ductal CIS (DCIS), and lobular CIS (LCIS). (b) Age-specific incidence rates for CIS and InvBC cases diagnosed during the years 1973–1980. (c) Age-specific incidence rates for CIS and InvBC cases diagnosed during the years 1990–2000.

for InvBC (4.8 versus 2.8 per 100,000 woman-years). RR for both CIS and InvBC were similar for low to high nuclear grade (RR = 1.4) and PR-positive to PR-negative expression (RR = 2.0). RR for ER-positive compared to ER-negative expression was lower for CIS (RR = 2.9) than for InvBC (RR = 3.2). However, RRs should be interpreted with caution, given the large amount of unknown data for some tumor categories.

Table 2 compared different architectural types of CIS: DCIS non-comedo ($n = 18{,}951$ or 53.6%), DCIS comedo ($n = 6616$ or 18.7%) and LCIS ($n = 4443$ or 12.6%). Median ages-at-diagnosis were significantly older ($p < 0.001$) for DCIS non-comedo (59 years) and DCIS comedo (58 years) than for LCIS (52 years). Tumor sizes-at-diagnosis were larger for DCIS non-comedo (1.0 cm) and DCIS comedo (1.3 cm) than for LCIS (0.6 cm). Black race was more common for DCIS non-comedo (RR = 1.0) than for other architectural types and least common for LCIS (RR = 0.6). LCIS was most likely to be associated favorable tumor characteristics including low nuclear grade (RR = 7.5), ER-positive expression (RR = 4.5), and PR-positive expression (RR = 3.1).

The age-specific incidence rate curve during the years 1990–2000 for CIS overall (total or all) was superimposed upon rates for InvBC overall, InvBC defined by ER-positive expression, and InvBC defined by ER-negative expression (Figure 2a). CIS rates increased rapidly until age 50 years, and then flattened. Rates for total InvBC and ER-positive InvBC increased rapidly until age 50 years, and then continued to rise at a slower rate for older women. Rates for ER-negative InvBC increased until age 50 years then flattened, as did rates for CIS.

Age-frequency density plots for all CIS, ER-negative InvBC, and ER-positive InvBC are shown in Figure 2b–d. CIS demonstrated bimodal age-frequency distribution with prominent early onset peak at age 50 years, as did ER-negative InvBC. On the other hand, ER-positive InvBC demonstrated bimodal age-frequency distribution with predominant late-onset peak frequency of 71 years, as did the age-frequency density plot for InvBC overall (chart not shown).

The age-specific incidence rate curve for CIS overall was superimposed upon rates for DCIS non-comedo, DCIS comedo, and LCIS architectural types in Figure 3a. Rates for DCIS non-

Table 1. Carcinoma *in situ* and invasive breast carcinoma from SEER's 9 Registry Database diagnosed during the years 1990–2000

	Carcinoma *in situ* (CIS)				Invasive breast carcinoma (InvBC)			
Total n = 223,908	35,347				188,561			
% of total cases	15.8%				84.2%			
Rate (SE)	25.8 (0.14)				134 (0.31)			
Median age (yrs)	59.0				62.2			
Mean tumor size (cm)	1.1				2.1			
Variable	N	Rate	SE	RR	N	Rate	SE	RR
Race								
White	29,448	26.3	0.2	1.0	160,942	138.8	0.3	1.0
Black	2870	22.8	0.4	0.9	15,328	120.4	1.0	0.9
Other	2707	21.8	0.4	0.8	11,510	92.9	0.9	0.7
Unknown	322				781			
Pathology								
Morphology								
Duct non-comedo	18,951	13.8	0.1	1.0	141,850	101.0	0.27	1.00
Duct comedo	6616	4.8	0.1	0.4	3818	2.8	0.05	0.03
Lobular	4443	3.3	0.1	0.2	15,393	10.9	0.09	0.11
Other or unknown	5337				27,500			
Nuclear grade								
High	5800	4.2	0.1	1.0	58,650	42.1	0.2	1.0
Low	7951	5.8	0.1	1.4	84,270	60.0	0.2	1.4
Other or unknown	21,596				45,641			
Hormone receptors								
ER								
ER-negative	1290	0.9	0.03	1.0	34,364	24.8	0.1	1.0
ER-positive	3770	2.7	0.05	2.9	113,400	80.6	0.2	3.2
Other or unknown	30,287				40,797			
PR								
PR-negative	1623	1.2	0.03	1.0	47,712	34.2	0.2	1.0
PR-positive	3254	2.4	0.04	2.0	96,332	68.7	0.2	2.0
Other or unknown	30,470				44,517			

Key: Median age-at-diagnosis in years; mean tumor size-at-diagnosis in centimeters; rate, age-adjusted (2000 US standard) incidence rate per 100,000 woman-years; SE, standard error; RR, rate ratio where a given characteristic is compared to a reference rate with an assigned value of 1.0; ER, estrogen receptor; PR, progesterone receptor.

comedo and comedo rose rapidly until age 50 years, then flattened, as did rates for CIS overall. On the other hand, rates for LCIS increased rapidly until age 50 years, and then declined sharply. Age-frequency density plots for DCIS and LCIS are shown in Figure 3b–d. DCIS non-comedo and comedo showed bimodal age-frequency distribution with a prominent early onset peak at age 51 and 50 years, respectively. On the other hand, LCIS demonstrated a pronounced unimodal peak frequency at age 50 years. The shape of the age distribution curves for CIS overall was unaffected by known or unknown race, nuclear grade, and ER expression (Figure 4a–c).

Discussion

Most breast carcinomas are thought to arise (or evolve) through a single biologic continuum or sequence extending from preinvasive to invasive

Table 2. Carcinoma *in situ* cases (CIS, $n = 35{,}347$) by architectural type from SEER's 9 Registry Database diagnosed during the years 1990–2000

	DCIS non-comedo				DCIS comedo				LCIS			
Total CIS, $n = 35{,}347$	18,951				6616				4443			
% of total CIS cases	53.6%				18.7%				12.6%			
Rate (SE)	13.8 (0.1)				4.8 (0.1)				3.3 (0.1)			
Median age (yrs)	59 years				58 years				52 years			
Mean tumor size (cm)	1.0 cm				1.3 cm				0.6 cm			
Variable	N	Rate	SE	RR	N	Rate	SE	RR	N	Rate	SE	RR
Race												
White	15,461	13.7	0.1	1.0	5658	5.0	0.1	1.0	3929	3.4	0.1	1.0
Black	1632	13.1	0.3	1.0	478	3.8	0.2	0.7	317	2.2	0.1	0.6
Other	1680				451				119			
Unknown	178				29				78			
Pathology												
Nuclear grade												
High	2856	2.1	0.04	1.0	2050	1.5	0.03	1.0	24	0.02	0.004	1.0
Low	5614	4.1	0.06	1.9	598	0.4	0.02	0.3	190	0.14	0.010	7.5
Other or unknown	10,481				3968				4229			
Hormone receptors												
ER												
ER-negative	653	0.5	0.02	1.0	479	0.3	0.02	1.0	50	0.04	0.005	1.0
ER-postive	2135	1.5	0.03	3.2	770	0.6	0.02	1.6	223	0.17	0.011	4.5
Other or unknown	16,163				5367				4170			
PR												
PR-negative	828	0.6	0.02	1.0	571	0.4	0.02	1.0	64	0.05	0.01	1.0
PR-positive	1844	1.3	0.03	2.2	641	0.5	0.02	1.1	203	0.15	0.01	3.1
Other or unknown	16,279				5404				4176			

Key: CIS, carcinoma *in situ*; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; Median age-at-diagnosis in years; Mean tumor size-at-diagnosis in centimeters; Rate, age-adjusted (2000 US standard) incidence rate per 100,000 woman-years; SE, standard error; RR, rate ratio where a given characteristic is compared to a reference rate with an assigned value of 1.0; ER, estrogen receptor; PR, progesterone receptor.

breast carcinoma, with every invasive breast carcinoma (InvBC) developing from a preexisting carcinoma *in situ* (CIS) [15]. Although the CIS to InvBC sequence provides a useful conceptual framework for scientific discovery, prevention and treatment strategies, it possibly oversimplifies a very complex biologic process. For example, many CIS lesions may not progress to InvBC, and some invasive tumors might arise directly within a background of normal appearing breast epithelium [16,17]. Some malignant lesions may even revert to preinvasive phenotypes [18].

If CIS was an obligate precursor for every InvBC, we would expect incidence patterns consistent with an evolutionary sequence, as for other epithelial tumors [14,19–21]. That is, (1) preinvasive disease prevalence would be greater than invasive disease incidence [19], (2) rising incidence for a curative progenitor would be associated with subsequent declining invasive tumors [20], (3) age distribution for the preinvasive and invasive components would follow a linear sequence [14, 19,20], and (4) tumor characteristics would progress from bad to worse with malignant transformation [21]. However, distinct incidence patterns among CIS and InvBC cases in the SEER database were difficult to reconcile with an obligate evolutionary sequence.

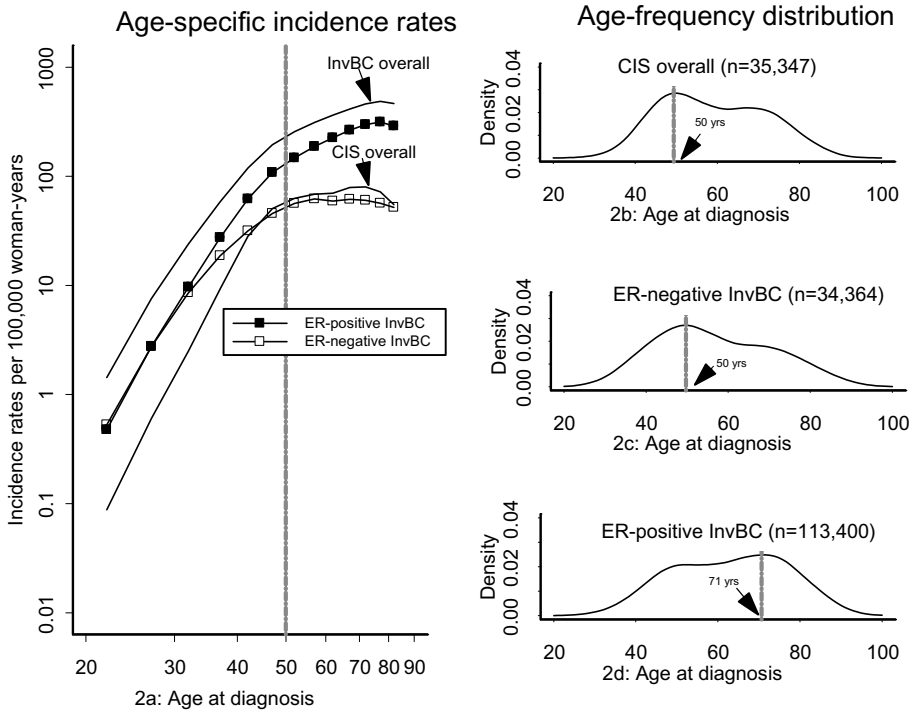

Figure 2. Age-specific incidence rates and age-frequency distribution for carcinoma *in situ* (CIS) overall, invasive breast carcinoma (InvBC) overall, and InvBC defined by ER expression for cases diagnosed during the years 1990–2000. (a) Age-specific incidence rates for CIS overall superimposed upon rates for InvBC overall, InvBC defined by ER-positive and ER-negative expression. (b) Age-frequency distribution for CIS overall. (c) Age-frequency distribution for InvBC defined by ER-negative expression. (d) Age-frequency distribution for InvBC defined by ER-positive expression.

First, with the possible exception of comedocarcinoma (4.8 and 2.8 per 100,000 for *in situ* and invasive comedocarcinomas, Table 1); there was not enough CIS to account for all InvBC. The rapid rise in CIS during the 1980s (Figure 1a) undoubtedly resulted from increases in surveillance, with screening mammography now being the greatest risk factor for CIS [22]. However, nearly 75% of women age ≥40 years receive biennial screening mammography in the United States [23], and yet, the incidence for CIS has remained less than one-fifth the incidence for InvBC (25.8 compared to 134 per 100,000 woman-years, Table 1).

Notably, breast autopsy studies suggest 20% cumulative lifetime risk for CIS [24], which is 48% higher than the estimated lifetime risk for being diagnosed with InvBC [25]; but how would we account for undetected or undiscovered CIS with approximately 75% screening prevalence? Some 'undiscovered' CIS might transform to InvBC without mammographically visible microcalcifications, clinical or physical symptoms. A proportion of CIS might be hidden among cases coded as InvBC by SEER. Some 'undetected' preinvasive lesions may not be histologically recognizable as CIS. Nonetheless, given that only a fraction of CIS will progress to InvBC [26–28], even these autopsy estimates may not provide enough CIS for all InvBC.

Second, since surgical excision or mastectomy is curative for nearly all CIS [29,30], early detection and removal of CIS with subsequent reductions in InvBC would provide compelling evidence for an evolutionary sequence. However, despite 660% increase for CIS during the last three decades (Figure 1a), total InvBC also rose. CIS now accounts for 15.8% of all newly diagnosed breast carcinomas (Table 1), but InvBC did not fall an equivalent amount. Alternately, CIS may be an obligate precursor for some but not all subtypes of InvBC [31,32]. For example, rates for *in situ* comedocarcinoma rose 53% (from 3.0 to 4.6 per 100,000 woman-years) as rates for invasive come-

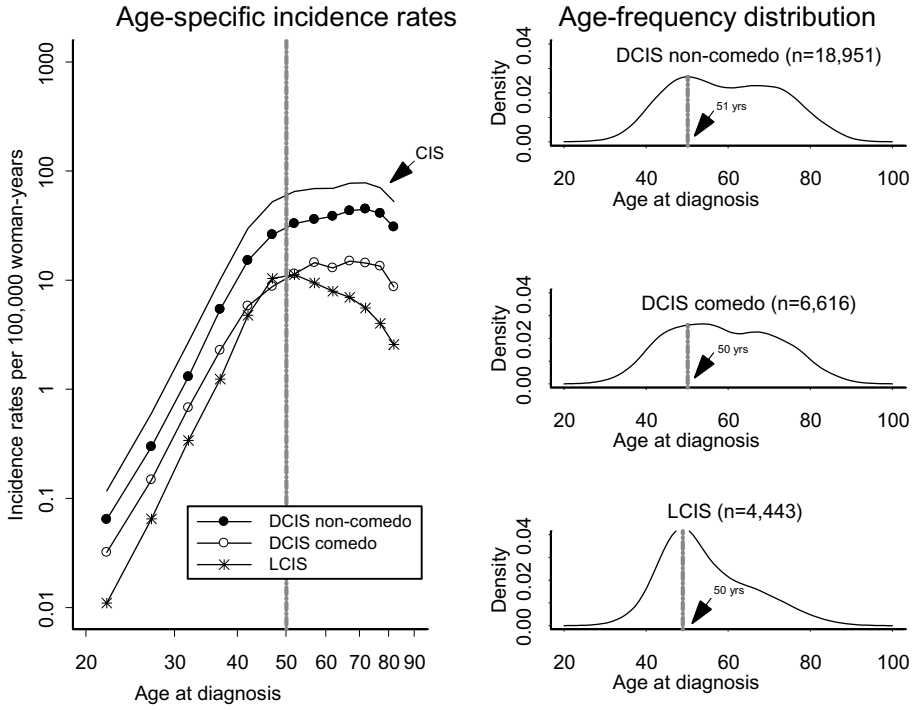

Figure 3. Age-specific incidence rates and age-frequency distribution for carcinoma *in situ* (CIS) overall, ductal CIS (DCIS, non-comedo and comedo) and lobular CIS (LCIS) for cases diagnosed during the years 1990–2000. (a) Age-specific rates for CIS superimposed upon rates for DCIS (non-comedo and comedo) and LCIS. (b) Age-frequency distribution for DCIS non-comedo. (c) Age-frequency distribution for DCIS comedo. (d) Age-frequency distribution for LCIS.

docarcinoma fell by 55% (from 3.3 to 1.5 per 100,000 woman-years) during the years 1990–2000. On the other hand, rates for non-comedocarcinomas did not change by similar amounts during this same time period.

Third, unlike all other epithelial tumors [10, 14], age distributions for *in situ* and invasive breast carcinomas did not follow a linear sequence. That is, the age-specific incidence curve for CIS increased rapidly until age 50 years then flattened, whereas age-specific rates for InvBC overall increased rapidly until age 50 years then rose at a slower rate. These age-specific patterns were apparent before and after widespread screening mammography (Figure 1b and c).

Additionally, the age-specific rate pattern for CIS was unaffected by ER expression (Figure 4c), but differed for InvBC defined by ER-positive and -negative expression (Figure 2a). Concordant age-specific rate curves for ER-positive and -negative breast carcinomas was first described for inflammatory and medullary InvBC [6–8], but to our knowledge, have not been described for CIS.

Notably, age-specific rates that failed to rise after age 50 years implied that carcinogenic factors operating early in reproductive life had greater impact upon CIS overall and ER-negative InvBC than upon InvBC overall and ER-positive InvBC. On the other hand, incidence rate curves that rose continuously with aging suggested that accumulated lifetime exposures or risk factors were more important for InvBC overall and ER-positive InvBC.

Age-frequency density plots also confirmed a more direct link with CIS overall and ER-negative InvBC than with ER-positive InvBC (Figure 2b–d). For example, the CIS bimodal age-frequency distribution with its predominant early onset peak at age 50 years was virtually superimposable with the age-frequency distribution of ER-negative InvBC. The two most common types of CIS (DCIS and LCIS) also appeared tightly linked to premenopausal hormonal exposures (Figure 3a), albeit more so for LCIS than for DCIS. The rates for DCIS increased rapidly until age 50 years then flattened, whereas rates for LCIS increased rapidly

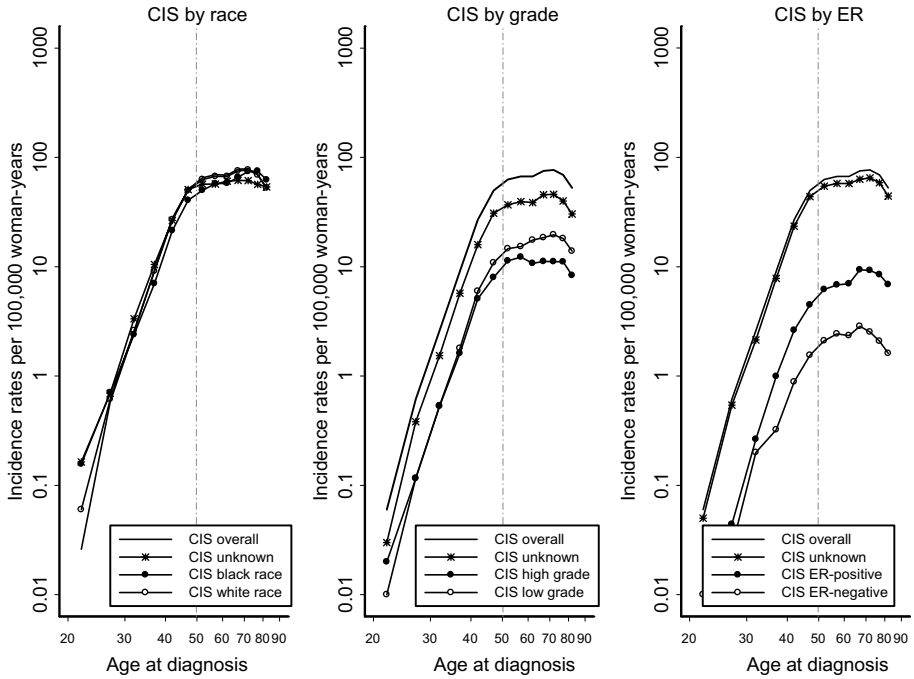

Figure 4. Age-specific incidence rates for carcinoma *in situ* (CIS) by (a) race, (b) nuclear grade, and (c) estrogen receptor (ER) expression.

until age 50 years then declined sharply. Parenthetically, a falling age-specific incidence rate curve cannot be reconciled with an evolutionary model of carcinogenesis.

Further clues regarding the distinct age distributions for CIS and InvBC can be obtained from mammographic, surgical, forensic and randomly selected autopsy studies. Among 1,179 mammography-derived breast tumors, Evans et al detected higher relative incidence of CIS compared to InvBC for women age <50 years (46.6%) than for women age ≥50 years (36.6%) [33]. Other investigators also have noted decreasing relative incidence of screened-derived CIS alone or in combination with InvBC among women ≥50 years [34,35]. Upon review of 11,760 surgical biopsies, Page et al identified low-grade DCIS among 28 women whose lesions were originally classified as benign [27]. Nine of these 28 women (32%) developed InvBC at a constant rate over the next 30 years [28]. This long-term constant relative risk is consistent with the 'flat' portion of the age-specific rate curves among older women with CIS overall (Figure 2a). In a series of 110 consecutive forensic autopsies among young and middle-aged women, Nielson et al. observed the greatest prevalence of preinvasive breast lesions for women between the ages of 40–49 years [36]. Alpers and Wellings also observed greater prevalence of CIS among younger than older women in 185 randomly selected autopsy specimens, commenting "that at least some CIS may be dependent upon a premenopausal hormonal milieu for their continuing existence" [37]. Conversely, Kramer and Rush concluded that CIS was infrequent among elderly women, after reviewing autopsy results from both breasts for 70 women ≥70 years of age [38,39]. In total, all of these studies as well as our own SEER observations suggest that advancing age is a greater risk factor for InvBC than for CIS (Figure 2a) [32,40].

Finally, tumor characteristics did not progress from CIS to InvBC (Table 1), as expected with a sequential model of carcinogenesis [41,42]. The term 'tumor progression' is credited to Petyon Rous who described the process whereby tumors evolved from 'bad to worse' (or favorable to unfavorable) [21]. In the context of a CIS to InvBC sequence, tumor characteristics should evolve from low to high grade or from hormone receptor-positive to hormone receptor-negative expression. However, RRs for low to high grade and PR-po-

sitive to PR-negative expression were identical among CIS and InvBC cases, i.e., there was no progression. Moreover, ER-negative expression was relatively more common for CIS than for InvBC. Given that most breast carcinomas were once thought to evolve through multistep dedifferentiation, we would have expected an opposite phenotypic drift [43], i.e., ER-positive expression should have been more common for CIS than for InvBC. However, a single progression model for breast carcinogenesis has not been supported by this analysis, our previous population-based studies [1,5–9], or modern molecular genetic techniques [44,45].

Alternatively, a branching evolutionary model may exist for breast carcinogenesis, as recently reviewed [46]. Indeed, carcinogenic pathways seemed to differ for InvBC defined by ER-negative and ER-positive expression, as suggested by divergent age-specific rate curves (Figure 2a). On the other hand, identical age-specific rate curves suggested similar etiology for all CIS, irrespective of estrogen receptor expression (Figure 4c).

The strength of this study was its large-scale population-based design. Limitations included lack of histopathologic slide review by a single pathologist or panel of pathologists, incomplete and non-standardized data for estrogen receptor expression, and absent data on menopausal status as well as other factors, such as method of detection that could impact results. Absent central slide review is an important concern. However, while there is acknowledged diagnostic variation among surgical pathologists for certain morphologic subtypes of InvBC, the distinction between CIS and InvBC is much less variable [47,48]. ER analysis was not carried out in a centralized laboratory, but CIS patterns did not vary by ER-positive, ER-negative, or ER-unknown expression (Figure 4c). SEER did not record menstrual history, but age 50 years is an established proxy for menstrual status [49]. Finally, given that most CIS is now mammographically derived; ideally, our results should have been adjusted for screening patterns [22]. Unfortunately, SEER did not record method of detection.

With that said, distinct incidence patterns for *in situ* (mostly mammographically derived) and invasive breast carcinomas have possible etiologic implications. Specifically, there was not enough CIS to account for all InvBC, even though nearly 75% of women age ≥40 years now receive screening mammography. Distinct age distribution and tumor characteristics for CIS and InvBC were difficult to reconcile with an obligate evolutionary model for every InvBC, with early life events having greater impact upon CIS than upon InvBC overall. Alternatively, multiple InvBC pathways may coexist with as of yet undefined relationships to screen-derived CIS. Further analytic studies clearly are needed to better decipher the different incidence patterns among *in situ* and invasive breast carcinomas; because if CIS is an obligate precursor for every InvBC, current screening strategies may be inadequate. On the other hand, if CIS is not an obligate precursor for all InvBC [31, 45], the clinical significance of screen-derived CIS is uncertain [35].

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